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1 **How effective are weight loss interventions for improving fertility in women and men**
2 **who are overweight or obese? A systematic review and meta-analysis of the evidence.**

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5
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8
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12 **Running title:** Do weight loss interventions improve fertility?

13 **AUTHOR:** there is a limit of 50 characters for the running title. Is this alternative acceptable?

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16 Table of Contents

17 **AUTHOR:** the table of contents does not appear to agree with the text. Only first (e.g.
18 **Introduction, Methods**) and second level headings (e.g. *Criteria for considering studies for*
19 *this review*) can be included in the Table of Contents (although third etc. level headings are
20 allowed in the main text). The styles used for headings in the main text should be consistent
21 and only second level headers included here. Please would you recheck and edit both the
22 main text and Table of Contents accordingly? Thank you.

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37 Description of interventions

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42 Studies involving male infertility participants

43 Discussion

44 Conclusions

45

46 **Abstract**

47

48 **BACKGROUND**

49 The prevalence of obesity is increasing worldwide, with a corresponding increase in overweight
50 and obese patients referred with infertility. This systematic review aimed to determine whether
51 non-surgical weight reduction strategies result in an improvement in reproductive parameters
52 affected by obesity, e.g. delayed time to pregnancy, oligozoospermia and azoospermia. No prior
53 reviews have examined this within the general fertility population, or in both sexes.

54

55 **OBJECTIVE AND RATIONALE**

56 Our objective was to answer the question: "In overweight and obese women, men and couples
57 seeking fertility treatment, what non-surgical weight loss interventions have been used, and
58 how effective are they at weight loss and improving reproductive outcomes?"

59

60 **SEARCH METHODS**

61 An electronic search of MEDLINE, EMBASE and the Cochrane Library was performed for studies
62 published between [AUTHOR: correct?] January 1966 and March 2016. Text word and MESH
63 search terms used related to infertility, weight, and barriers to weight loss. Inclusion criteria
64 were: an intervention to change lifestyle evaluated in any study design in participants of either
65 gender with an unfulfilled desire to conceive. Studies were excluded if they included
66 participants not attempting pregnancy, with illnesses that might cause weight fluctuations, or
67 studies evaluating bariatric surgery. Two reviewers performed data extraction and quality

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assessment using the Cochrane Risk of Bias Tool for randomised trials, and a ratified checklist (ReBIP) for non-randomised studies.

OUTCOMES

A total of 40 studies were included, of which 14 were RCTs. Primary outcomes were pregnancy, live birth rate and weight change. In women, reduced calorie diets and exercise interventions were more likely than control interventions to result in pregnancy [Risk Ratio 1.59, 95% CI (1.01, 2.50)], and interventions resulted in weight loss and ovulation improvement, where reported. Miscarriage rates were not reduced by any intervention.

WIDER IMPLICATIONS

Overweight and obese persons seeking fertility should be educated on the detrimental effects of fatness and the benefits of weight reduction, including improvement in pregnancy rates. A combination of a reduced calorie diet, by reducing fat and refined carbohydrate intake, and increased aerobic exercise should form the basis of programmes designed for such individuals. A lack of randomised studies in men and couples, and studies evaluating barriers to undertaking weight loss in infertile populations is evident, and future research should examine these issues further.

Key words: infertility, obesity, weight loss, systematic review, diet, exercise

Introduction

Overweight is defined by the World Health Organization (WHO) (World Health Organization, 2016) as a BMI ≥ 25 kg/m², and obesity as ≥ 30 kg/m². The prevalence of obesity is increasing worldwide (World Health Organization, 2016), with more than 600 million obese adults, including 15% of women, in 2014 - double the prevalence reported three decades earlier. Infertility is defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Hochschild *et al.*, 2009; National Institute for Health and Clinical Excellence, 2013). Using this definition, infertility affects about 1 in 7 couples in the UK, which is similar to an estimate of prevalence in the USA (Thoma *et al.*, 2013). An increasingly overweight and obese population has led to a greater proportion of individuals with high BMI being evaluated in infertility settings (Vahratian and Smith, 2009).

BMI has been associated with delayed conception in women in a dose-dependent fashion (Gesink Law *et al.*, 2007; Wise *et al.*, 2013; Wise *et al.*, 2010). It is thought to produce anovulation (Zain and Norman, 2008; Klenov and Jungheim, 2014), which results in menstrual irregularity (Hartz *et al.*, 1979; Zain and Norman, 2008); impairment of oocyte development (Klenov and Jungheim, 2014) and quality (Carrell *et al.*, 2001; Metwally *et al.*, 2007); and it also has direct effects on the endometrium (Bellver *et al.*, 2011). With ovulation induction (OI) treatment, higher doses of medications (Dickey *et al.*; Balen *et al.*, 2006a) and a longer period of stimulation (Balen *et al.*, 2006b) are required with a higher BMI. With IVF, the chances of achieving a pregnancy decrease with each unit increase in BMI (Ferlitsch *et al.*, 2004), and it is thought that implantation rates are lower in obese women (Bellver *et al.*, 2010; Styne-Gross *et al.*, 2005). An increased risk of miscarriage following IVF has also been reported (Maheshwari *et al.*, 2007).

114 Obesity may affect male fertility in a dose-dependent manner (Sallmen *et al.*, 2006). Postulated
115 mechanisms include increased testicular temperature with prolonged sitting (Hammoud *et al.*,
116 2012), and increased oestrogen production in fat with disruption of the hypothalamo-pituitary-
117 gonadal axis (Schneider *et al.*, 1979; Shukla *et al.*, 2014). Some studies have suggested reduced
118 sperm concentration and motility (Hammiche *et al.*, 2012; Hakonsen *et al.*, 2011; Sermondade
119 *et al.*, 2013), and lower clinical pregnancy rates with IVF (Keltz *et al.*, 2010; Umul *et al.*, 2015)
120 with increasing male adiposity. Where both partners are obese, greater difficulty achieving
121 pregnancy is expected (Ramlau-Hansen *et al.*, 2007).

122
123 Patients attending for fertility treatments are often advised to optimize their weights to
124 improve outcomes, and in some cases to access assistance with funding (National Institute for
125 Health and Clinical Excellence, 2013; Farquhar and Gillett, 2006; Infertility Network UK, 2015)
126 or to reduce the risks of obstetric complications (The Royal Australian and New Zealand College
127 of Obstetricians and Gynaecologists, 2011).

128
129 The purpose of this systematic review was to investigate first whether weight loss interventions
130 for infertile patients achieve their goal in reducing weight, and second whether they result in
131 improved fertility outcomes. A prior systematic review of 11 studies in women (Sim K.A. *et al.*,
132 2014) focussed on assisted reproduction only and used a much more limited search for studies
133 up until 2014. Our review used an extensive search until 2016 and presents data from 40
134 studies with women and men with infertility, not just patients requiring assisted reproduction.

135

136 **Methods**

137

138 This systematic review was undertaken according to a pre-specified protocol.

139

140 ***Criteria for considering studies for this review***

141

142 *Types of studies*

143 We included intervention studies in overweight or obese participants with any design and any
144 duration of follow-up.

145

146 *Types of participants*

147 Participants could be of either sex. They were required to have both infertility, defined by an
148 unfulfilled desire to conceive of any duration or attendance for infertility investigations or
149 treatment, and a prescribed period of attempt at weight loss. A BMI ≥ 25 kg/m² was used to
150 define overweight, and ≥ 30 kg/m² to define obesity (World Health Organization, 2016);
151 participants were required to be at least overweight. Morbid obesity was defined by BMI ≥ 40
152 kg/m². Studies were excluded if participants were not actively attempting pregnancy, or had an
153 illness or eating disorder that might result in weight fluctuation.

154

155 *Types of interventions*

156 Any intervention for weight loss allowed inclusion, for example prompt for weight reduction,
157 dietary modification, exercise, psychological or behavioural counselling, or the drug orlistat.
158 Bariatric surgery was not included. Alternative or control interventions were included where
159 evaluated in included studies.

160

161 *Types of outcome measures*

162 Primary outcomes were weight change, achievement of pregnancy, and live birth, the latter
163 defined as the complete expulsion or extraction from its mother of a product of fertilisation,
164 which, after such separation, breathes or shows any other evidence of life such as heart beat,
165 umbilical cord pulsation, or definite movement of voluntary muscles, irrespective of whether
166 the umbilical cord has been cut or the placenta is attached (National Institute for Health and
167 Clinical Excellence, 2013).

168
169 Secondary outcomes were BMI change; waist circumference change (North American
170 Association for the Study of Obesity *et al.*, 2000); miscarriage, defined as a loss of pregnancy
171 before 23+6 weeks of gestation (Anonymous , 2012); ovulation improvement, with anovulation
172 defined by suboptimal rise in LH, or a below-threshold serum progesterone level taken in the
173 mid-luteal phase of the menstrual cycle (National Institute for Health and Clinical Excellence,
174 2013); improvement in menstrual regularity, with irregular cycles defined as outside the range
175 of 26-36 days (National Institute for Health and Clinical Excellence, 2013); and time to
176 conception.

177
178 ***Search methods for identification of studies***
179

180 The dates searched were 1 January 1966 to 19 March 2016. No restriction was placed on
181 language of origin, or publication status and studies could be included regardless of whether
182 they had been published (AUTHOR: please would you clarify what you mean by 'status' here?).

183 The electronic databases used were MEDLINE, EMBASE and the Cochrane Library. Additional
184 studies were identified through review of the references of the retrieved papers, contact with
185 study authors, and online searching of Google and Google Scholar (Google Inc., Mountain View,
186 CA, USA). The search strategy used for MEDLINE and EMBASE is given in the Supplementary
187 Data (AUTHOR: we tend not to include Appendices, therefore these data have been divided and
188 renamed as supplementary files.)

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Data collection and analysis

Selection of studies

The titles and abstracts obtained were screened by one author (DB). To verify the process of selection, the titles and abstracts for the year 2000 were independently screened by DB and AA, with full agreement with respect to papers to be included or excluded. Thus full text versions of all relevant papers were retrieved by DB for further scrutiny by both reviewers. Any disagreement between the two as to which studies to include was resolved by discussion.

Data collection process

Data were extracted by one reviewer (DB), and checked by a second (AA). Discrepancies were resolved by discussion between the reviewers, and a third reviewer (SB) was available for referral as necessary. Study authors were contacted as required for missing data or clarification.

For each included study, the information collected included study design; methods; location, setting and time period; information about the participants (demographics, infertility diagnosis, BMI, eligibility criteria); drop-outs; the types of interventions assessed and their descriptions; and outcomes, including pregnancy, live births, weight or BMI change, miscarriage, ovulation and menstrual change. For men, semen analysis parameters were captured. **(AUTHOR: please would you re-state those outcomes here, for clarity? Thank you.)**. Any data on barriers to weight loss were also captured. Data on costs and cost-effectiveness were sought but not found.

Assessment of risk of bias in individual studies

RCTs were assessed for their methodological quality using the Cochrane Risk of Bias Tool (Higgins *et al.*, 2011).

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216 Non-randomised studies were assessed using a checklist developed for the Review Body for
217 Interventional Procedures (ReBIP) (64)(AUTHOR: please would you use the correct format of
218 citation?). The ReBIP is an independent review body that carries out systematic reviews for the
219 National Institute for Health and Care Excellence's Interventional Procedures Programme. The
220 checklist was adapted from several sources (Verhagen *et al.*, 1998; Khan *et al.*, 2001; Downs
221 and Black, 1998), and has been used in many systematic reviews. It includes assessment of
222 sample selection; clarity of inclusion and exclusion criteria; baseline comparability of
223 participants; consecutive selection of patients; prospective data collection; clarity of
224 intervention descriptions; experience of person administering the intervention;
225 appropriateness of staff, place and facilities where participants were treated; consideration of
226 important incomes on clinical effectiveness, cost-effectiveness, or learning curves; use of
227 objective outcome measures; blinding of outcome assessment; adequacy of duration of follow-
228 up to detect important effects on outcomes of interest; information provision on dropouts, and
229 their similarity to completers; identification of important prognostic factors; and adjustment of
230 analyses for confounding factors.

231
232 *Summary measures*

233 Results were summarised descriptively. In the outcome summary tables, numbered rankings
234 are provided in an effort to demonstrate which study interventions reported more favourable
235 outcomes, with a lower number indicating a better outcome. Meta-analysis was undertaken
236 where possible. Risk ratios (RR) and mean differences with 95% CI between groups are
237 reported.

238
239 *Synthesis of results*

240 Data were imported into Review Manager Version 5.3.5 (The Cochrane Collaboration, Oxford,
241 UK) for quantitative synthesis. A random effects, rather than a fixed effect model, was used for

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242 meta-analysis, owing to unavoidable population and intervention heterogeneity, as anticipated
243 in interventions for weight loss.

244

245 *Assessment of heterogeneity*

246 Statistical heterogeneity was investigated by visual inspection of forest plots, the Q-test (with
247 $p < 0.1$ implying statistical heterogeneity) and by examining the I^2 statistic (Higgins and
248 Thompson, 2002), where a result $> 50\%$ was taken to indicate substantial statistical
249 heterogeneity.

250

251 *Sensitivity analyses*

252 Sensitivity analysis was planned to compare randomised trials judged to be at low risk of bias
253 for allocation concealment or randomisation with those judged to be at higher risk of bias;
254 however, the small numbers of trials precluded this.

255 **Results**

256

257 ***Outcome of the search***

258

259 Details of the selection process for studies is summarised in the PRISMA flow diagram (Figure

260 1) ***(AUTHOR: the quality of this figure still seems poor. If possible, please can you send to me a***

261 ***higher quality file?)*** Seventeen study authors were contacted for clarification or further

262 information; ten provided helpful further information.

263

264 Full details of all the studies and interventions are provided in Supplementary Table SI. There
265 were 14 RCTs, six non-randomised studies with comparison groups (NRCTs), and twenty cohort
266 studies with interventions. Ten studies took place in Australia, seven in the USA, three each in
267 Italy and the Netherlands, and two in Denmark. One each came from Belgium, Brazil, Canada,
268 Egypt, France, Germany, India, Iran, Jordan, Pakistan, Russia, Saudi Arabia, Slovakia, Turkey and
269 the UK. Three studies were multi-centre.

270

271 Enrolment varied from eight participants (Faure *et al.*, 2014) to 577 (Mutsaerts *et al.*, 2016).
272 Attrition rates ranged from 10.6% (Mutsaerts *et al.*, 2016) to 66.7% (Turner-McGrievy *et al.*,
273 2014).

274

275 ***Description of populations***

276

277 Mean age of study groups varied from 25 years (Lazurova *et al.*, 2004) to 35.4 years (Chavarro
278 *et al.*, 2012). Ethnicity was reported in six papers, with between 55% (Turner-McGrievy *et al.*,
279 2014) and 87.5% white (Mutsaerts *et al.*, 2016).

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281 Duration of infertility, where reported, ranged from a mean of 19.5 months (Palomba *et al.*,
282 2008) to 11 years (Aliyeva *et al.*, 1993). Some studies addressed women with any infertility
283 history. Others centred on women undergoing fertility treatments or planning to start
284 immediately following the intervention. Some were exclusively catered to persons with
285 polycystic ovary syndrome (PCOS), with the syndrome defined by Rotterdam 2004 consensus
286 criteria (ESHRE and Group, ASRM-Sponsored PCOS Consensus Workshop, 2004) in ten cases,
287 National Institutes of Health (NIH) criteria (Zawadzki and Dunaif, 1992) in one case, ultrasound
288 appearance of the ovaries in two cases, and not specified in five cases. One study used PCOS as
289 an exclusion criterion (Moran *et al.*, 2003).

290
291 In eight studies, patients were anovulatory, and in seven studies patients had irregular
292 menstrual cycles. Three papers were centred on patients who were resistant to clomiphene
293 citrate for ovulation induction.

294
295 The lowest mean BMI was 24.5 kg/m² (Chavarro *et al.*, 2012), and the highest was 44 kg/m²
296 (Mahoney, 2014; Hakonsen *et al.*, 2011).

297
298 Two studies were centred on men. One had participants with sperm DNA fragmentation who
299 were overweight or obese (Faure *et al.*, 2014), while the other examined obese men only
300 (Hakonsen *et al.*, 2011). One study examined a weight loss intervention in couples (Homan *et*
301 *al.*, 2012).

302

303 ***Description of interventions***

304

305 Table 1 provides brief details of the types of interventions tested. In general, interventions were
306 poorly described, with insufficient detail to allow their replication. Where described, most
307 reducing diets followed healthy eating principles by reducing fat and refined carbohydrate

308 intake. Where available, studies described calorie intakes ranging from 1000 to 2000kcal/d
309 (depending on body size), apart from three studies that tested very low calorie diets as part of
310 their reducing diets (Tsagereli 2006, Kiddy 1992, van Dam 2004) and one that tested a very low
311 carbohydrate ketogenic diet (Mavroupolos 2005). If physical activity advice or programmes
312 were incorporated into interventions, they were generally for aerobic exercise. There was no
313 clear evidence that any particular regime was more effective for weight loss, providing there
314 was a weight reduction diet prescribed.

315
316 Five of the 16 interventions incorporating both a dietary and physical activity component
317 provided some part of the intervention in a group setting. Only two interventions were
318 described involving couples. One study (Chavarro *et al.*, 2012) tracked participants' weights
319 after administering a lifestyle questionnaire. While this is not strictly a weight-loss intervention,
320 we have included it with the other cohort studies, because there is evidence that weight loss
321 occurs with enrolment in studies tracking weight, even with minimal intervention (Waters *et al.*,
322 2012; Johns *et al.*, 2016).

323
324

325 **Quality of studies**

326
327 The quality of the studies included was variable. For full details of risk of bias assessment for all
328 the randomised studies please see Supplementary Table SII. ~~The quality of the studies included~~
329 ~~was variable.~~ Three of fourteen RCTs had four or five out of seven domains with low risk of bias,
330 e.g. allocation concealment, incomplete outcome data, but the Lifestyle trial (Mutsaerts *et al.*,
331 2016) stood out as the one with best quality. All studies were of high risk of bias with respect to
332 blinding of participants to treatment allocation, and all had low risk of bias in at least two
333 domains. Five of 26 non-randomised studies, having eight to nine of 14 domains with low risk of

334 bias, were judged to be good quality. [Full details of the risk of bias assessment for the non-](#)
335 [randomised studies are given in Supplementary Table SIII.](#)

336
337 ***Studies involving female infertility participants***

338
339 *Pregnancy*

340 Aggregated data from six RCTs show that women who received a combination of a reducing diet
341 and exercise had higher pregnancy rates than those who underwent standard care **AUTHOR: is**
342 **there a word missing? Please would you recheck the sense here? Thank you.** 238/434 (54.8%)
343 versus 221/443 (49.9%); RR 1.59, 95% CI (1.01, 2.50) (Figure 2). The trial by Mutsaerts *et al*
344 (2016)) contributed significantly to the heterogeneity, $I^2=71\%$ and its exclusion in a post-hoc
345 sensitivity analysis reduced I^2 to 0%. Although the numbers of participants in other RCTs were
346 too few for any meaningful conclusions to be drawn, a very small trial was unable to
347 demonstrate any advantage of diet alone, while another suggested that orlistat might be
348 beneficial. The results of an NRCT (Clark et al, 1998) support the result of the meta-analysis
349 favouring diet and exercise. The study by Koning et al (2015) did not show any advantage
350 associated with motivational interviewing.

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Table 2 details the reproductive outcomes for all included studies. Diet and exercise studies without control populations achieved rates that were comparable to those included in the meta-analysis.

Live births

Data from five RCTs (Figure 3) did not favour diet and exercise over standard care in terms of live birth rates which were 48.9% (195/399) versus 46.8% (190/406) respectively; RR 1.54, 95% CI (0.93, 2.56). Mutsaerts et al (Mutsaerts *et al.*, 2016) again contributed significantly to the heterogeneity, $I^2=69\%$. Its exclusion in a post-hoc sensitivity analysis reduced I^2 to 0%, and resulted in diet and exercise having a statistical advantage, RR 1.86, 95% CI (1.25, 2.77). The NRCT (Clark *et al.*, 1995; Clark *et al.*, 1998) also favoured the intervention arm, 45/67 (67.2%) versus no treatment (0/20); RR 28.10, 95% CI (1.81, 436.85). Motivational interviewing was also not associated with an increased live birth rate.

Table 2 details live birth rates for all included studies. Women in studies on diet and exercise without control groups had lower success rates than those included in the meta-analysis. Khaskheli et al (Khaskheli *et al.*, 2013), who did not provide details of their intervention, reported a 37.6% (32/85) livebirth rate, while Crosignani et al, (Crosignani *et al.*, 2003), who administered a 1200 kcal/day diet along with aerobic exercise, achieved a 24.2% (8/33) rate. The numbers of participants in the other studies included in Table 2 were too few for any meaningful conclusions to be drawn.

372 *Spontaneous and IVF conceptions*

373 Pooled data from RCTs (Figures 4 and 5) show that, reducing diets and exercise were not
374 associated with a higher chance of spontaneous conception [28.3% (86/304) versus 15.9%
375 (50/315); RR 2.20, 95% CI (0.98, 4.93)].

376

377 *Miscarriages*

378 A combination of a reducing diet and exercise was associated with a pooled miscarriage rate of
379 13.4 per hundred women (48/357) or 23.3% of pregnancies (48/206) (Figures 6 and 7). The
380 control arm had a pooled miscarriage rate of 8.7 per hundred women (31/355) or 15.6% of
381 pregnancies (31/199). This shows no benefit of diet and exercise [combined RR 0.96, 95% CI
382 (0.89, 1.04) per woman and RR 0.91, 95% CI (0.91, 0.82, 1.01) per pregnancy]. Miscarriage rates
383 in the other studies on diet and exercise vary widely (Table 2).

384

385 *Ovulation*

386 One RCT (Palomba *et al.*, 2010) found a 37.5% (12/32) ovulation improvement with a
387 combination of reducing diet and exercise, while its control group had a 9.3% (3/32)
388 improvement rate; RR 4.00 95% CI (1.25, 12.84) (Figure 8). An NRCT, also using diet and
389 exercise, ~~that~~ had the highest rate of improvement of all included studies in its intervention
390 group. [AUTHOR: again, does this sentence read correctly? Please would you recheck?], 89.6%
391 (60/67), while none of the participants in the control group saw improvement; RR 37.37, 95%
392 CI (2.41, 578.65).

393

394 One RCT (Kumar and Arora, 2014) compared the use of 120mg of orlistat twice daily and a
395 lifestyle modification programme with use of the lifestyle programme alone. The orlistat group
396 had a 50% (15/30) rate of ovulation, while the control group had a 6.7% (2/30) rate; RR 7.50,
397 95% CI (1.88, 29.99).

398

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399 One RCT (Legro *et al.*, 2015) compared the proportions of total clomiphene treatment cycles
400 that were ovulatory in each group. The group whose treatment was preceded by diet and
401 exercise advice and the oral contraceptive pill (OCP) had the best ovulation rate, 67.1% (94/140),
402 while the lifestyle alone group and control (OCP alone) group had rates of 60.3% (82/136) and
403 46.1% (71/154) respectively.

404
405 Another RCT (Thomson *et al.*, 2008) randomised its participants, who had PCOS, to receive an
406 energy-restricted high-protein diet alone (DO), combined with aerobic exercise (DA), or
407 combined with both aerobic and resistance exercise (DC). DO saw a 50% (6/12) improvement
408 in ovulation, DA a 50% (3/6) improvement, and DC a 42.8% (3/7) improvement.

409
410 Table 2 shows the ovulation rates in cohort studies of diet without controls. One study using a
411 very low calorie diet (van Dam *et al.*, 2004) had a relatively good ovulation improvement rate,
412 60% (9/15). Other studies had comparatively low rates, including one using a hypocaloric 1434
413 kcal/day diet (Thomson *et al.*, 2009) which achieved a 19.2% (10/52) rate, and another
414 (Turner-McGrievy *et al.*, 2014) which saw no improvement using either a low-calorie diet
415 (LCD) **[AUTHOR: please define LCD]** or a vegan diet. One study compared a hypocaloric high
416 protein diet to structured exercise training (SET) (Palomba *et al.*, 2008), and achieved a 25%
417 (5/20) improvement rate with diet, and a 65% (13/20) improvement with exercise.

418
419 A study comparing ovulation improvement in women receiving acupuncture to those receiving
420 an unspecified diet (Aliyeva *et al.*, 1993) had a 55% (11/20) improvement with the former, and
421 46.7% (28/60) improvement in the latter; RR 1.18, 95% CI (0.73, 1.90).

422
423 *Menstrual irregularity*
424 In clomiphene citrate resistant PCOS women, a single trial (Palomba *et al.*, 2010), showed that
425 hypocaloric diet and exercise was significantly more likely to result in menstrual improvement,

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426 than observation only: 34.4% (11/32) versus 9.3% (3/32); RR 3.67, 95% CI (1.13, 11.92)
427 (Figure 9). Other studies without control groups also suggest that diet and exercise were
428 associated with improvement in menstrual regularity (Table 2). There were no RCTs evaluating
429 the role of dietary interventions alone or motivational interviewing in regulating menstrual
430 cyclicity. Data from observational and often uncontrolled studies of other interventions show
431 variable levels of success (Table 2).

432

433 *Oocyte retrieval*

434 Data from a single RCT (Figure 10) suggest that a low glycaemic index diet (Becker *et al.*, 2015)
435 could improve oocyte yield in IVF. The mean (SD) number of oocytes in women in the
436 intervention arm was 7.75 (5.39), compared to 4.18 (SD 3.01) in controls; mean difference -
437 3.57, 95% CI (-6.87, -0.27).

438

439 *Time to conception*

440 The Lifestyle trial (Mutsaerts *et al.*, 2016) reported that the median time to conception (TTC)
441 resulting in a term live birth was 7.2 months (interquartile range (IQR) 2.6, 12.0) in the
442 intervention group, who underwent a multidisciplinary programme based on diet and exercise,
443 versus 5.2 (IQR 2.4, 10.1) in the control group, who were allowed fertility treatment from the
444 start (P=0.06). An RCT comparing energy-restricted low protein and high protein diet groups
445 who both received exercise instruction (Moran *et al.*, 2003) reported a 4-5 week TTC regardless
446 of group. A cohort study which advised women to lose 10% of their body weight (Kort *et al.*,
447 2013; Kort *et al.*, 2014) found that those who met the target had a mean TTC of 227 days, while
448 those who had not had a mean of 231 days.

449

450 *Weight loss*

451 Aggregated data from RCTs suggest that a combination of a reducing diet and exercise resulted
452 in greater weight loss than that achieved in control groups (Figure 11); mean difference -3.98 kg

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453 (95% CI -4.85, -3.12). Diet alone was also shown to be more effective in a small RCT; mean
454 difference -5.23kg (95% CI -7.42, -3.04) (Becker *et al.*, 2015).

455
456 In non-randomised trials, Clark *et al.* (Clark *et al.*, 1998) reported significantly greater weight
457 loss from diet and exercise; mean difference -9.00kg (95% CI -10.88, -7.12). Two non-
458 randomised trials testing motivational interviewing also found greater weight loss; mean
459 difference -3.21kg (95% CI -5.93, -0.49kg). Changes in weight, BMI and waist circumference for
460 other studies are provided in Table 3. Generally results are not inconsistent with studies with
461 either randomised or non-randomised control groups.

462

463 ***Comparisons with metformin***

464

465 *Pregnancy*

466 Three small RCTs evaluated lifestyle interventions versus metformin (Figure 12). None was able
467 to show any superiority of metformin over the alternative intervention, but it is difficult to be
468 confident about these outcomes owing to the small sample sizes involved.

469

470 *Ovulation*

471 Two small RCT of diet or drug treatment (Figure 13) were unable to show any benefit over
472 metformin. Details of other studies are in Table 2.

473

474 *Menstrual irregularity*

475 Metformin did not appear to improve menstrual regularity in a number of small trials
476 comparing it to diet and exercise with or without drug treatment, diet alone or acarbose (Figure
477 14). Details of other studies are in Table 2.

478

479 *Weight loss*

480 Weight, BMI and waist circumference changes for studies comparing metformin with lifestyle
481 interventions are provided in Table 3.

482 AUTHOR: please would you mention Supplementary Table SIII (Quality assessment for non-
483 randomised studies) at the appropriate place in the Results section? (Please renumber the
484 Supplementary Tables if order in text requires it.) Thank you.

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485 **Summary of the key findings in infertile women**

486

487 In overweight and obese infertile women, weight loss is associated with improved chances of
488 becoming pregnant, and possibly spontaneous conception pre-IVF. Ovulation and menstrual
489 irregularity are also aided. There appears to be no significant difference between weight loss
490 interventions and controls with respect to rates of miscarriage and IVF conceptions. The few
491 studies that included metformin showed no significant difference between weight loss
492 interventions and the drug for achieving pregnancy or improvement in ovulation status;
493 similarly there was no difference between the two groups in menstrual improvement.

494

495 **Barriers to weight loss in infertile women**

496

497 Very little has been reported regarding the perceived barriers to weight loss in overweight and
498 obese infertile women. Two of the included studies attempted in some way to evaluate these.
499 In the trial by Thomson et al (Thomson *et al.*, 2008), 104 participants were allocated to receive
500 an energy restricted diet only (D0), the same diet combined with five sessions of aerobic
501 walking and jogging exercise per week (DA), or the diet combined with aerobic and resistance
502 training exercises (DC), where resistance exercise replaced two of the aerobic sessions (110)

503 (AUTHOR: please would you use the correct format for the citation? Thank you.) Forty-three of
504 the participants in the trial (D0=13, DA=11 and DC=19) completed a validated Exercise
505 Benefits/Barriers Scale at weeks 0, 10 and 20 (Thomson *et al.*, 2016). This was to determine
506 their perceptions of the benefits and barriers to participation in exercise. The scale included 43

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507 items with statements related to ideas about exercise and a four-point Likert scale, with 4 =
508 strongly agree, 3 = agree, 2 = disagree and 1 = strongly disagree. At baseline, the statements
509 with the highest agreement were: “exercise tires me” [mean (SD), 2.86 (0.71)]; “exercise is hard
510 work for me [2.79 (0.67)], and “I am fatigued by exercise” [2.60 (0.62)]. Those with the lowest
511 agreement were: “my family members do not encourage me to exercise” [1.56 (0.59)], “my
512 spouse does not encourage exercising” [1.63 (0.70)], and “I think people in exercise clothes look
513 funny” [1.72 (0.59)].

514
515 Barrier scores were reduced by week 10 in this study, regardless of treatment allocation, with
516 no further reduction by week 20 ($P \leq 0.001$). Time expenditure and physical exertion as
517 perceived barriers saw a significant reduction ($P \leq 0.003$), while family discouragement saw no
518 change ($P = 0.6$).

519
520 Participants in the study by Galletly et al (Galletly *et al.*, 1996), in addition to completing a 24-
521 week programme with weekly meetings comprising 1 hour of exercise and 1 hour of dietary and
522 psychiatric counselling, completed the Rosenberg Self-Esteem Scale and the General Hospital
523 Anxiety and Depression Scale at the start and end of the study. At baseline, those who dropped
524 out before the end of intervention exhibited higher anxiety ($p < 0.02$) and depression scores
525 ($p < 0.069$), and lower self-esteem scores ($p < 0.056$) than those who completed. Completion was
526 associated with a significant improvement in self-esteem ($p < 0.0001$) and depression ($p < 0.006$),
527 and a non-significant reduction in anxiety scores.

528
529 Based on what little evidence is available, overweight infertile women appear most deterred
530 from exercise by the perception that it causes fatigue and is hard work. These perceptions, as
531 well as depression, seem to decrease with continuation of an exercise programme. Very few
532 women seem to be discouraged from exercise by family members. Those women who
533 discontinue exercise would appear to be more anxious and/or depressed at the outset.

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Studies involving male infertility participants

Achievement of pregnancy, live birth rate, and Improvement in sperm DNA integrity

One cohort study (Faure *et al.*, 2014) administered a nutritionist-led personalised dietary programme of an unreported nature coupled with exercise, aimed at reducing intra-abdominal fat over a 3-8 month period, to eight men who had significant abdominal fat and at least 25% sperm DNA fragmentation and unexplained infertility (Table 4). The partners of all eight achieved pregnancy, three naturally and five through IUI, and all went on to have live births. Six who allowed their semen samples to be analysed both before and after the intervention all had an improvement in the degree of sperm DNA fragmentation.

AUTHOR: could the following sections be edited to avoid repeating most of the data that are shown in Table 4, as we try to minimise such repetition in the results section? Thank you,

Improvement in semen analysis parameters

A cohort of 44 men with BMI 33-61 kg/m² underwent a programme based on a healthy diet and daily exercise (Hakonsen *et al.*, 2011). Semen analyses before and afterward were compared in 27 men, and the results were as shown in Table 4.

The group with 3.5-12.1% weight loss (Group 1, n=9) saw a mean change in sperm concentration of -11 million/ml (95% CI -49, +27). The group with 12.2-17.1% (Group 2, n=9) loss had a mean change of +19 million/ml (95% CI -23, 61). The group with 17.2-25.4% loss (Group 3, n=9) had a mean change of +17million/ml (95% CI -24, 58).

Group 1 saw a mean change in progressive sperm motility of -2%, 95% CI (-15,11). Group 2 had a mean change +4%, 95% CI (-10, 18). Group 3 had a mean change +11%, 95% CI (-3, 25).

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561 ~~Group 1 saw a mean change in normal sperm morphology of 0%, 95% CI (-2, 4). Group 2 had a~~
562 ~~mean change of +1%, 95% CI (-3, 4). Group 3 had a mean change of +4%, 95% CI (1, 7).~~

563

564 *Change in weight*

565 ~~The cohort study by Hakonsen et al (Hakonsen et al., 2011) achieved median weight change~~
566 ~~22kg, range -4 to 39 kg. The cohort study by Faure et al (Faure et al., 2014) achieved a mean~~
567 ~~weight reduction of 4.40 (SD 5.0 kg). Table 4 also summarises the weight loss achieved in both~~
568 ~~studies.~~

569

570 *Summary*

571 The relative paucity of studies in overweight and obese men seeking fertility has made it
572 difficult to draw firm conclusions regarding the benefits of weight loss. However, improvements
573 in sperm concentrations, motility and normal morphology have been suggested, though these
574 have not been statistically significant. Improvement in sperm DNA integrity has also been
575 suggested, and this might be linked to an improved live birth rate.

576

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577 **Discussion**

578

579 ***Key findings***

580

581 The present systematic review and meta-analysis found that the weight loss interventions,
582 particularly diet and exercise, improved pregnancy rates and ovulatory status. A trend toward
583 more natural pregnancies, but not IVF pregnancies, occurred. Miscarriage rates were unaffected
584 by weight loss interventions and, as reports of higher oocyte yield and improved menstrual
585 regularity are based on single trials, further research is needed before firm conclusions can be
586 made. A lack of RCTs in men and couples, and of studies evaluating barriers to undertaking
587 weight loss in overweight and obese infertile populations, is evident. The quality of the studies
588 we included was variable, but the one with the lowest risk of bias was the Lifestyle trial
589 (Mutsaerts *et al.*, 2016), whose intervention also ranked highly for both pregnancy and live
590 birth rates.

591

592 ***Women***

593

594 ***Pregnancies and live births***

595 Weight loss interventions, particularly those with reducing diets and exercise, were more likely
596 than controls to result in pregnancy. Live births were reported by ~~only a few~~ relatively fewer
597 studies. **[AUTHOR: correct?]**, usually involving women undergoing fertility treatments such as
598 OI or IVF. Data from studies predating the Lifestyle trial in 2016 (Mutsaerts *et al.*, 2016)
599 suggested that diet and exercise combinations were superior to standard care, but inclusion of
600 this trial changed this. Those in the intervention arm underwent a 6-month programme based
601 on diet and exercise, prior to undergoing 18 months of fertility treatments. Those in the control
602 arm commenced fertility treatments immediately. The primary outcome was vaginal birth of a
603 healthy singleton of at least 37 weeks' gestation within 24 months after randomisation. The trial

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604 was well conducted, with low risk of bias. This was the largest study in the review, and it carried
605 substantial weight during meta-analysis. The results deviated from the trend exhibited by the
606 preceding trials, resulting in marked increase in heterogeneity. It is possible that the results
607 might have been different if the control group underwent 6 months of no intervention
608 observation prior to 18 months of treatment. The trial found that significantly more women in
609 the intervention group had ongoing pregnancies from natural (AUTHOR: the term natural' is
610 usually preferred throughout but I leave the final decision to you.) conception than the control
611 group, consistent with our other findings.

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612
613 Studies reporting the highest pregnancy and live birth rates were not necessarily those with
614 highest weight loss. Clark et al, had a high live birth rate of 67.2% in the diet and exercise arm of
615 their NRCT, while also achieving one of the highest weight changes, mean -10.2kg (SD 4.3)
616 (Clark *et al.*, 1995; Clark *et al.*, 1998). On the other hand, the intervention arm of the Mutsaerts
617 et al (2016) RCT reported a live birth rate of 53.2%, but only achieved a mean weight change of
618 -4.4 kg (SD 5.8).

619
620 *Miscarriages*

621 Studies with some of the lowest rates of weight loss reported fewer miscarriages in their
622 intervention arms, but the data are insufficient to draw conclusions (Tables 2 and 3).

623
624 *Ovulation*

625 Weight loss interventions, regardless of their nature, were significantly more likely than control
626 interventions to achieve ovulation in anovulatory women. Improvements were not necessarily
627 greatest in those studies achieving the greatest weight loss.

628

629 *Menstrual irregularity*

630 A single RCT suggested that diet and exercise were significantly more likely to improve
631 menstrual cycles than a control intervention (Palomba *et al.*, 2010). High rates of menstrual
632 improvement were seen in studies with good weight or BMI reduction. Qublan et al (2007), for
633 example, with a 1200-1400 kcal diet in their RCT, had a 61.9% menstrual improvement and
634 achieved one of the better BMI reductions, with a mean change of -4.8 kg/m².

635

636 *Spontaneous and IVF conceptions*

637 Studies included women expected to proceed to in-vitro treatments after a period of weight
638 loss. Many women were able to conceive without further assistance through weight loss alone.
639 All interventions showed an improved rate of spontaneous conception in comparison to a
640 control. There was however no significant difference between interventions and controls when
641 it came to IVF conceptions. Similar spontaneous conception rates were seen regardless of type
642 of intervention and/or amount of weight lost.

643

644 *Change in weight, BMI and waist circumference*

645 No class of intervention was consistently better in achieving reduction in weight compared to
646 others. Trials with longer interventions and follow-up sometimes suffered from higher rates of
647 study drop-out, for example 20.4% in the 12-month Sim et al RCT (Sim *et al.*, 2014a) and 10.6%
648 in the 6-month Mutsaerts et al RCT (Mutsaerts *et al.*, 2016), both of which mainly had diet and
649 exercise. Others had no dropout: Karlsen et al after 7-8 months (Karlsen *et al.*, 2013) and
650 Koning et al after 6 months (Koning, 2015), and both included motivational interviewing. This
651 suggests that enhancing motivation plays a key role in compliance. Programmes with strict
652 dietary and exercise modifications may be more likely to see discontinuation. The study with
653 the most weight lost, the cohort study by Mavropoulos et al (Mavropoulos *et al.*, 2005), utilised

654 a very restrictive diet for 6 months, and had very low recruitment (n=11) and a high rate of
655 drop-out (58.5%).

656

657 *Metformin*

658 The meta-analyses showed that weight loss interventions have a non-significant advantage over
659 metformin with respect to achievement of pregnancy or improvement of ovulation status. There
660 was also no significant difference in menstrual regularity improvement. In light of these
661 findings, and the gastro-intestinal side-effects common with metformin (Kumar and Arora,
662 2014; Qublan *et al.*, 2007), lifestyle interventions should remain the first line therapy for
663 improvement in ovulation and menstruation.

664

665 *Interventions in infertile men*

666

667 There was very little evidence available to judge the effectiveness of weight reduction strategies
668 in men, and this is an area ripe for future research. The two studies both utilised a diet and
669 exercise combination, with neither providing adequate details of the intervention.

670

671 *Types of diet*

672

673 As expected, the dietary interventions used were based on caloric restriction, and were usually
674 consistent with weight reduction advice from national guidelines (National Clinical Guideline
675 Centre, 2014; Dietz *et al.*, 2015). It is hard to say, based on the data obtained, whether any
676 particular degree of restriction was superior for achievement of weight loss, particularly given
677 the frequent pairing of diet with exercise. Some of the RCTs used individualized diets, tailoring
678 caloric deficit to baseline weight (Becker *et al.*, 2015; Duval *et al.*, 2015b). Others mentioned a
679 hypocaloric range within which dietary intakes would fall (Kumar and Arora, 2014; Qublan *et*
680 *al.*, 2007; Thomson *et al.*, 2008; Turner-McGrievy *et al.*, 2014), generally between 1200 and

1800 kcal/day. Dieticians were used to assist with dietary advice in a few cases (Duval *et al.*, 2015b; Turner-McGrievy *et al.*, 2014; Thomson *et al.*, 2008; Mutsaerts *et al.*, 2016). The RCT with the lowest recruitment and highest discontinuation rate used a vegan diet in one of its study arms (Turner-McGrievy *et al.*, 2014), suggesting poor acceptance.

Types of exercise

The majority of exercise interventions sought to increase weekly aerobic activity in participants in order to increase caloric expenditure. The most frequent feature seen in the RCTs was an increase in the number of steps or amount of walking by participants (Duval *et al.*, 2015b; Karimzadeh and Javedani, 2010; Legro *et al.*, 2015; Mutsaerts *et al.*, 2016; Sim *et al.*, 2014a; Thomson *et al.*, 2008). Fewer RCTs (AUTHOR: correct, or studies?) included strength or resistance training (Karimzadeh and Javedani, 2010; Moran *et al.*, 2011b; Thomson *et al.*, 2008), and this was always in addition to the basic aerobic approach. Thomson *et al.* found that addition of resistance training did not result in a significantly different weight loss in their RCT of diet alone, diet with aerobic exercise, or diet with aerobic and resistance exercise (Thomson *et al.*, 2008). Physical activity interventions were in some cases individualised (Duval *et al.*, 2015a; Moran *et al.*, 2011a) and in others in the form of group sessions (Moran *et al.*, 2003), with occasional use of a kinesiologist (Duval *et al.*, 2015a) or physiotherapist (Kumar and Arora, 2014).

Types of weight loss medication

The use of weight loss drugs is contraindicated during pregnancy (Department of Veterans Affairs, 2014), and the studies using them aimed to reduce weight prior to attempting pregnancy. One trial (Legro *et al.*, 2015) recommended barrier contraception during its intervention. Oral medications used in the studies included orlistat, a lipase inhibitor;

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708 sibutramine, a selective serotonin and norepinephrine reuptake inhibitor; and acarbose, an
709 alpha-glucosidase inhibitor shown to induce modest weight loss, though not suitable for weight
710 maintenance (Hauner *et al.*, 2001). Of these, sibutramine, which has been withdrawn in Europe
711 and the USA but is still available on the internet, has been shown in a large study to have a risk
712 of cardiovascular defects in unborn infants (Källén, 2014), while the same study showed no risk
713 of birth defects from orlistat use. The safety of acarbose in pregnancy is not established. Orlistat
714 was shown to be superior to a control with respect to achievement of pregnancy and ovulation
715 in a single study (Kumar and Arora, 2014). Until further evidence is available, lifestyle
716 interventions should still be considered the first line therapy, with drug use reserved for
717 monitored trials.

718

719 ***Strengths and limitations of the review***

720

721 This review has added to the scope of the systematic review by Sim *et al.* (2014b) by going
722 beyond examining overweight and obese women undergoing fertility treatment to encompass
723 individuals of both genders, and couples, from a variety of infertility circumstances undergoing
724 non-surgical weight loss programmes. A wide search strategy meant that we were thus able to
725 capture 40 studies, in comparison to the 11 in that review (Sim *et al.*, 2014b). Author contact,
726 initiated with 17 study authors, was another strength, as this allowed unreported information
727 to be gained, and clarification of unclear information. Nevertheless, we cannot exclude
728 publication bias, where studies with less positive outcomes remain unreported.

729

730 ***Clinical recommendations***

731

732 Overweight and obese persons seeking fertility should be educated on the effects of being
733 overweight or obese on the ability to achieve pregnancy, and the benefits of weight reduction,
734 including improvement in pregnancy rates, and a reduced need for OI and IVF.

735

736 A combination of a reduced calorie diet, which is not overly restrictive, and aerobic exercise,
737 intensified gradually, should form the basis of programmes designed for such individuals. As
738 compliance is key to success, coached sessions of achievable frequency, e.g. weekly, for up to 6
739 months, should be considered. Motivational interviewing techniques might also be useful. An
740 advantage of fertility care is that couples are catered to, and dual enrolment may result in better
741 adherence, as partners tend to motivate each other.

742

743 ***Research recommendations***

744

745 Future research would ideally be in the form of large multi-centre RCTs including both women
746 and men, ideally couples, attending fertility clinics and having at least one partner with a BMI
747 within the overweight or obese range. Based on the data from RCTs of diet and exercise
748 examined here, we estimate that a trial would require over 454 participants to detect a
749 difference of 15% in pregnancy rates (90% power, $p < 0.05$, control pregnancy rate 50%,
750 intervention rate 65%). This figure does not take account of losses to follow-up, and would need
751 to be considerably inflated, depending on drop-out rates in feasibility and pilot work.

752

753 A reasonable control intervention would be the administration of dietary and exercise advice
754 only-, to be undertaken for a brief period only (AUTHOR: correct?), to reduce persons allocated
755 to this arm feeling as though their fertility treatments were being delayed with no intervention.
756 Similar durations employed between intervention and control groups prior to starting fertility
757 treatments would allow for fair comparisons with respect to weight loss and reproductive
758 outcomes.

759

760 A long duration of follow-up, spanning decades, might answer further questions, including
761 whether obstetric problems related to weight such as gestational diabetes or caesarean rates

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762 might be reduced in imminent or future pregnancies. The permanency of lifestyle changes made
763 while attempting fertility might also be established, as well as their impact on family members,
764 and the maintenance of weight loss in the long term. ~~The role of epigenetic changes might also~~
765 ~~be explored.~~ (AUTHOR: although important, and you are discussing possible future research
766 here, this subject has not been mentioned so far and seems a little unrelated to the overall
767 approach here. It is also unclear what particular studies you would perform, therefore I suggest
768 removing it, which would not detract from the discussion. If you agree, please edit accordingly?
769 Thank you.)

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771 **Conclusions**

772
773 Non-surgical weight reduction strategies in the infertile have been shown to improve
774 reproductive outcomes in both men and women. Diet, exercise, a combination of the two,
775 weight-loss medication and motivational interviewing have all been efficacious in reducing
776 obesity. In women, weight loss from diet and exercise is associated with improved chances of
777 becoming pregnant, with a trend toward improved live birth rate. Ovulation and menstrual
778 irregularity are also aided. At present there appears to be no significant difference between
779 weight loss interventions and control interventions with respect to rates of miscarriage and IVF
780 conceptions. Well-designed RCTs should also shed light on the effect of weight loss on numbers
781 of oocytes retrieved and other parameters in IVF cycles, and on TTC, as well as the role of
782 interventions in couples. In men, improvements in sperm concentrations, motility and normal
783 morphology have been suggested, as well as in sperm DNA integrity, but further high quality
784 research is needed to confirm these findings and demonstrate improvement in live birth rates in
785 their partners.

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789 Sim, Amany Salama, Rebecca Thomson, Cherrie Galletly, and Hanno Pijl.

790 **Authors' roles**

791 Dr Damian Best was involved in design and conduct of the review, data analysis, drafting the
792 manuscript and critical discussion. Professor Alison Avenell was involved in the design and
793 conduct of the review, supervised data analysis, checked data extraction, and was involved in
794 manuscript revision and critical discussion. Professor Siladitya Bhattacharya was involved in
795 the design of the review and contributed to manuscript revision and critical discussion.

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800

801 **Conflict of interest**

802 None declared.

803

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1033 **Figure legends**

1034 **AUTHOR:** I have files for a Figure 1 (PRISMA chart in tiff format) plus Figures 2-14 in eps

1035 format. The legends below are for only 13 figures. Please would you recheck the figure

1036 numbering/titles?

1037 Figure 1. PRISMA flow diagram illustrating the process of selection of studies for inclusion in the

1038 systematic review. **AUTHOR:** please would you provide a higher quality image for Production?

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1040 Figure 2. **AUTHOR:** it may be helpful to also state in all titles that these are Forest plots. Forest

1041 plot - Pregnancies associated with diet, diet and exercise, orlistat and motivational interviewing

1042 versus control.

1043

1044 Figure 3. Forest plot - Intervention versus control: live births.

1045 Figure 4. Forest plot - Intervention versus control: spontaneous conceptions.

1046 Figure 5. Forest plot - Intervention versus control: IVF conceptions.

1047 Figure 6. Forest plot - Intervention versus control: miscarriages for all participants enrolled.

1048 Figure 7. Forest plot - Intervention versus control: miscarriages for women who became

1049 pregnant.

1050 Figure 8. Forest plot - Intervention versus control: ovulation improvement.

1051 Figure 9. Forest plot - Intervention versus control: improvement of menstrual irregularity.

1052 Figure 10. Forest plot - Intervention versus control: oocytes retrieved per female participant.

1053 Figure 11. Forest plot - Intervention versus control: change in weight (kg).

1054 Figure 12. Forest plot - Intervention versus metformin: women who became pregnant.

1055 Figure 13. Forest plot - Intervention versus metformin: improvement in ovulation.

1056 Figure 14. Forest plot – Intervention versus metformin: improvement in menstrual irregularity

1057 per irregular menstruating female participant

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1059 **AUTHOR:** we tend not to include Appendices, therefore these data have been

1060 divided and renamed as supplementary files. The quality of the file for the

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1061 Supplementary Data (search strategy) is not high enough for Production, therefore
1062 please would you send to me a high quality file, eps or tiff format, and preferably at
1063 300dpi? Word and Powerpoint are acceptable if not pixelated or blurry at 400%. Thank
1064 you.

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Table 1. Types of interventions evaluated in studies of weight loss interventions and fertility in women and men who are overweight or obese.

| Reducing diet/healthy eating and exercise programme or advice | |
|---|---------|
| Duval <i>Duval et al</i> 2015 G | RCT |
| Karimzadeh <i>Karimzadeh et al</i> 2010 | RCT |
| Moran <i>Moran et al</i> 2011 | RCT |
| Mutsaerts <i>Mutsaerts et al</i> 2016 | RCT |
| Palomba <i>Palomba et al</i> 2010 G | RCT |
| Sim <i>Sim et al</i> 2014 G | RCT |
| Clark <i>Clark et al</i> 1998 G | Non-RCT |
| Crosignani <i>Crosignani et al</i> 2003 | Cohort |
| De Frène 2015 | Cohort |
| Faure <i>Faure et al</i> 2014 | Cohort |
| Galletly <i>Galletly et al</i> 1996a G | Cohort |
| Galletly <i>Galletly et al</i> 1996b G | Cohort |
| Hakonsen <i>Hakonsen et al</i> 2011 | Cohort |
| Hollman <i>Hollman et al</i> 1996 | Cohort |
| Khaskheli <i>Khaskheli et al</i> 2013 | Cohort |
| Mahoney <i>Mahoney et al</i> 2014 | Cohort |
| Miller <i>Miller et al</i> 2008 G | Cohort |
| Salama <i>Salama et al</i> 2015 | Cohort |
| Reducing diet/healthy eating, weight loss drugs, and exercise programme or advice | |
| Legro <i>Legro et al</i> 2015 | RCT |
| Lazurova <i>Lazurova et al</i> 2004 | Non-RCT |
| Kort <i>Kort et al</i> 2014 | Cohort |
| Reducing diet/health eating, or type of diet | |

| | |
|---|---------|
| Becker Becker <i>et al</i> 2015 | RCT |
| Moran Moran <i>et al</i> 2003 | RCT |
| Qublan Qublan <i>et al</i> 2007 | RCT |
| Turner-McGrievy Turner-McGrievy <i>et al</i> 2014 | RCT |
| Aliyeva Aliyeva <i>et al</i> 1993 | Non-RCT |
| Palomba Palomba <i>et al</i> 2008 G | Non-RCT |
| Awartani Awartani <i>et al</i> 2012 | Cohort |
| Kiddy Kiddy <i>et al</i> 1992 | Cohort |
| Mavropoulos Mavropoulos <i>et al</i> 2005 G | Cohort |
| Thomson Thomson <i>et al</i> 2009 | Cohort |
| Tsagareli Tsagareli <i>et al</i> 2006 | Cohort |
| Van Dam Van Dam <i>et al</i> 2004 | Cohort |
| Behavioural therapy, including motivational interviewing | |
| Karlsen Karlsen <i>et al</i> 2013 | Non-RCT |
| Koning Koning <i>et al</i> 2015 C | Non-RCT |
| Homan Homan <i>et al</i> 2012 | Cohort |
| Exercise programme | |
| Thomson Thomson <i>et al</i> 2008 G | RCT |
| Palomba Palomba <i>et al</i> 2008 | Non-RCT |
| Orlistat | |
| Kumar Kumar <i>et al</i> 2014 | RCT |
| Metformin | |
| Karimzadeh Karimzadeh <i>et al</i> 2010 | RCT |
| Kumar Kumar <i>et al</i> 2014 | RCT |
| Qublan Qublan <i>et al</i> 2007 | RCT |
| Sonmez Sonmez <i>et al</i> 2005 | RCT |
| Lazurova Lazurova <i>et al</i> 2004 | Non-RCT |
| Acarbose | |
| Sonmez Sonmez <i>et al</i> 2005 | RCT |
| Detailed lifestyle questionnaire | |

| Study ID | Intervention arm | | Pregnancies per participant | | % Live births per participant | | % Miscarriages per participant (fewer = better) | | % Miscarriages per pregnancy (fewer = better) | | % Improved ovulation per anovulatory participant | | % Improved menstrual irregularity / irregular menses per participant | | Time to conception per participant (less = better) | |
|--|---|----|-----------------------------|------|-------------------------------|------|---|-----|---|------|--|------|--|------|--|--|
| | | N | Rank | % | Rank | % | Rank | % | Rank | % | Rank | % | Rank | % | Rank | |
| Palomba Palomba <i>et al</i> 2008 | Exercise | 20 | 14 | 35.0 | | | 7 | 5.0 | 5 | 14.3 | 5 | 65.0 | | | | |
| Homan Homan <i>et al</i> 2012 | Motivational interviewing | 35 | 15 | 34.8 | | | 5 | 4.3 | 3 | 12.5 | | | | | | |
| Awartani Awartani <i>et al</i> 2012 | Weight reduction advised | 90 | 16 | 34.4 | | | | | | | | | | | | |
| Qublan Qublan <i>et al</i> 2007 | Diet | 24 | 17 | 33.3 | | | 4 | 4.2 | 3 | 12.5 | 10 | 50.0 | 11 | 61.9 | | |
| Legro Legro <i>et al</i> 2015 | Diet & exercise | 50 | 18 | 32.0 | 9 | 26.0 | 9 | 6.0 | 10 | 18.8 | 6 | 60.3 | | | | |
| Crosignani Crosignani <i>et al</i> 2003 | Diet & exercise | 33 | 19 | 30.3 | 10 | 24.2 | | | | | 8 | 55.6 | 6 | 66.7 | | |
| Aliyeva Aliyeva <i>et al</i> 1993 | Diet | 60 | 20 | 30.0 | | | | | | | 14 | 46.7 | 8 | 63.3 | | |
| Kiddy Kiddy <i>et al</i> 1992 | Very low calorie diet/Low calorie diet | 24 | 21 | 29.2 | 14 | 16.7 | 10 | 8.3 | 13 | 28.6 | | | 20 | 29.4 | | |
| Hollman Hollman <i>et al</i> 1996 | Diet & exercise | 35 | 22 | 28.6 | 12 | 22.9 | 8 | 5.7 | 11 | 20.0 | | | 3 | 80.0 | | |
| Legro Legro <i>et al</i> 2015 | Diet, exercise, oral contraceptive pill | 50 | 23 | 28.0 | 11 | 24.0 | 3 | 4.0 | 5 | 14.3 | 4 | 67.1 | | | | |
| Qublan Qublan <i>et al</i> 2007 | Metformin | 22 | 24 | 27.3 | | | 6 | 4.5 | 7 | 16.7 | 15 | 45.5 | 12 | 61.1 | | |
| Kumar Kumar <i>et al</i> 2014 | Metformin | 30 | 25 | 26.7 | | | | | | | 20 | 23.3 | | | | |
| Becker Becker <i>et al</i> 2015 | Diet | 14 | 26 | 21.4 | 13 | 21.4 | | | | | | | | | | |
| Karimzadeh Karimzadeh <i>et al</i> 2010 | Diet & exercise | 75 | 26 | 20.0 | | | | | | | | | 6 | 66.7 | | |
| Lazurova Lazurova <i>et al</i> 2004 | Metformin | 30 | 28 | 20.0 | | | | | | | | | 4 | 70.0 | | |
| Miller Miller <i>et al</i> 2008 | Diet & exercise | 12 | 29 | 16.7 | | | | | | | | | 1 | 83.3 | | |
| Karimzadeh Karimzadeh <i>et al</i> 2010 | Metformin & clomiphene | 88 | 30 | 14.8 | | | | | | | | | 10 | 62.5 | | |
| DeFrene 2015 | Diet & exercise | 23 | 31 | 13.0 | | | | | | | | | | | | |
| Karimzadeh Karimzadeh <i>et al</i> 2010 | Metformin | 90 | 32 | 12.2 | | | | | | | | | 13 | 55.6 | | |
| Salama Salama <i>et al</i> 2015 | Mediterranean diet & exercise | 58 | 33 | 12.1 | | | | | | | | | 9 | 62.8 | | |

| Study ID | Intervention arm | | Pregnancies per participant | | % Live births per participant | | % Miscarriages per participant (fewer = better) | | % Miscarriages per pregnancy (fewer = better) | | % Improved ovulation per anovulatory participant | | % Improved menstrual irregularity / irregular menses per participant | | Time to conception per participant (less = better) | |
|--|---|----|-----------------------------|------|-------------------------------|---|---|-----|---|-----|--|------|--|------|--|-----------|
| | | N | Rank | % | Rank | % | Rank | % | Rank | % | Rank | % | Rank | % | Rank | |
| Turner-McGrievy Turner-McGrievy <i>et al</i> 2014 | Low calorie diet | 9 | 34 | 11.1 | | | | | | | 22 | 0.0 | | | | |
| Palomba Palomba <i>et al</i> 2008 | Diet | 20 | 35 | 10.0 | | | 1 | 0.0 | 1 | 0.0 | 19 | 25.0 | | | | |
| Galletly Galletly <i>et al</i> 1996(a) | Exercise & advice | 96 | 36 | 9.4 | | | | | | | | | | | | |
| Moran Moran <i>et al</i> 2003 | High protein diet | 14 | 37 | 8.7 | | | | | | | | | 21 | 26.1 | 1 | 4-5 weeks |
| Lazurova Lazurova <i>et al</i> 2004 | Sibutramine, diet, exercise | 15 | 38 | 6.7 | | | | | | | | | 14 | 53.3 | | |
| Thomson Thomson <i>et al</i> 2008 | Diet & aerobic exercise | 31 | 39 | 6.3 | | | | | | | 10 | 50.0 | 17 | 42.9 | | |
| Moran Moran <i>et al</i> 2003 | Low protein diet | 14 | 40 | 4.3 | | | | | | | | | 22 | 22.7 | 1 | 4-5 weeks |
| Thomson Thomson <i>et al</i> 2008 | Diet | 30 | 41 | 3.3 | | | | | | | 10 | 50.0 | 24 | 21.4 | | |
| Palomba Palomba <i>et al</i> 2010 | Diet & exercise, Clomiphene | 32 | 42 | 3.1 | | | | | | | 18 | 37.5 | 19 | 34.4 | | |
| Thomson Thomson <i>et al</i> 2008 | Diet & aerobic & resistance exercise | 33 | 43 | 3.0 | | | | | | | 16 | 42.8 | 16 | 44.4 | | |
| Turner McGrievy 2014 | Vegan diet | 9 | 44 | 0 | | | | | | | 22 | 0.0 | | | | |
| Sonmez Sonmez <i>et al</i> 2005 | Acarbose | 15 | | | | | | | | | 2 | 86.7 | 5 | 69.2 | | |
| Sonmez Sonmez <i>et al</i> 2005 | Metformin | 15 | | | | | | | | | 3 | 80.0 | 2 | 80.0 | | |
| Van Dam Van Dam <i>et al</i> 2004 | Very low calorie diet | 15 | | | | | | | | | 6 | 60.0 | | | | |
| Thomson Thomson <i>et al</i> 2009 | Diet | 52 | | | | | | | | | 20 | 19.2 | 18 | 42.3 | | |
| Palomba Palomba <i>et al</i> 2010 | Diet & exercise | 32 | | | | | | | | | 21 | 12.5 | 25 | 12.5 | | |
| Mahoney Mahoney <i>et al</i> 2014 | Motivational interviewing, diet, exercise | | | | | | | | | | | | 23 | 22.2 | | |

Table 3. Weight reduction outcomes for women (lower numbers for ranking indicate better outcomes).

| Study ID | Intervention Arm | N | Mean Weight change (kg) Per Participant | | Mean BMI change (kg/m ²) Per Participant | | Mean Waist Circumference change (cm) Per Participant | |
|---|---|-----|---|---------------------------|--|--------------------------|--|---------------------------|
| | | | Rank | Change | Rank | Change | Rank | Change |
| Mavropoulos Mavropoulos et al 2005 | Low calorie ketogenic diet | 5 | 1 | -12.34 ± 6.37 | 8 | -4.0 | | |
| Hollman Hollman et al 1996 | Diet & exercise | 35 | 2 | -10.2 ± 7.9 | 10 | -3.4 (median) | | |
| Clark Clark et al 1998 | Diet & exercise | 67 | 3 | -10.2 ± 4.3 | 9 | -3.7 ± 1.6 | | |
| Thomson Thomson et al 2008 | Diet & aerobic exercise | 31 | 4 | -10.1 ± 5.6 | | | 1 | -11.7 ± 6.1 |
| Karlsen Karlsen et al 2013 | Motivational interviewing | 110 | 5 | -9.3 | 11 | -3.3 | | |
| Thomson Thomson et al 2009 | Diet | 52 | 6 | -9.0 ± 0.8 (SEM) | | | 4 | -10.4 ± 0.9 (SEM) |
| Thomson Thomson et al 2008 | Diet | 30 | 7 | -8.6 ± 6.0 | | | 3 | -10.8 ± 7.1 |
| Thomson Thomson et al 2008 | Diet & aerobic & resistance exercise | 3 | 8 | -8.6 ± 5.2 | | | 2 | -11.0 ± 6.3 |
| Moran Moran et al 2003 | High protein diet | 14 | 9 | -8.5 ± 1.1 | | | | |
| Kumar Kumar et al 2014 | Orlistat | 30 | 10 | -7.81 ± 0.66% | 4 | -8.12 ± 6.71% | | |
| Kumar Kumar et al 2014 | Metformin | 30 | 11 | -7.78 ± 0.57% (SEM) | 3 | -8.40 ± 0.65% (SEM) | 14 | -2.68 ± 0.16% (SEM) |
| Kiddy Kiddy et al 1992 | Very low calorie diet/low calorie diet | 24 | 12 | -6.9 ± 6.7 | | | | |
| Moran Moran et al 2003 | Low protein diet | 14 | 13 | -6.9 ± 0.8 (SEM) | | | | |
| Sim Sim et al 2014 | Diet & exercise | 26 | 14 | -6.6 ± 4.6 | 14 | -2.4 ± 1.6 | 6 | -8.7 ± 5.6 |
| Salama Salama et al 2015 | Mediterranean diet & exercise | 58 | 15 | -6.3 ± 20.8 | 16 | -2.37 ± 7.28 | 7 | -6.45 ± 14.13 |
| Legro Legro et al 2015 | Lifestyle | 50 | 16 | -6.2, 95% CI (-7.3, -5.3) | | | 8 | -6.3, 95% CI (-9.2, -3.4) |
| Galletly Galletly et al 1996(b) | Diet and exercise | 58 | 17 | -6.2 ± 4.5 | 13 | -2.4 ± 1.7 | | |
| Legro Legro et al 2015 | Diet, exercise, oral contraceptive pill | 50 | 18 | -6.1, 95% CI (-7.0, -5.2) | | | 9 | -6.2, 95% CI (-9.1, -3.3) |
| Tsagareli Tsagareli et al 2006 | Very low calorie diet | 6 | 19 | -5.6; Range -8.2 to -5.3 | 17 | -2.1; Range -1.8 to -3.2 | 5 | -10.0; Range -7 to -14 |
| Galletly Galletly et al 1996(a) | Diet & exercise | 96 | 20 | -5.2 ± 5.1 | | | | |
| Becker Becker et al 2015 | Diet | 14 | 21 | -4.51 ± 0.83 (SEM) | | | 15 | -1.31 ± 10.5 |
| Palomba Palomba et al 2010 | Diet & exercise, Clomiphene | 32 | 22 | -4.42 ± 9.22 | 12 | -2.64 ± 4.26 | 11 | -4.92 ± 5.87 |

| Study ID | Intervention Arm | | Mean Weight change (kg) Per Participant | | Mean BMI change (kg/m ²) Per Participant | | Mean Waist Circumference change (cm) Per Participant | |
|---|---|-----|---|--|--|--|--|--|
| | | N | Rank | Change | Rank | Change | Rank | Change |
| Mutsaerts Mutsaerts et al 2016 | Diet & exercise | 280 | 23 | -4.4 ± 5.8 | 21 | -1.3 (Median) IQR (-2.5, -0.07) | | |
| Koning Koning et al 2015 | Motivational interviewing | 102 | 24 | -4.3 ± 0.8 (SEM) | 20 | -1.4 ± 0.3 (SEM) | | |
| Palomba Palomba et al 2010 | Diet & exercise | 32 | 25 | -4.21 ± 8.56 | 15 | -2.39 ± 3.54 | 12 | -3.84 ± 6.35 |
| Moran Moran et al 2011 | Diet & exercise | 18 | 26 | -3.8 ± 3.0 | 19 | -1.4 ± 1.1 | 10 | -5.3 ± 4.6 |
| Mahoney Mahoney et al 2014 | Motivational interviewing, diet, exercise | 9 | 27 | -3.18 ± 2.27 | 24 | -0.7 ± 7.31 | | |
| Turner-McGrievy Turner-McGrievy et al 2014 | Vegan diet | 9 | 28 | -2.1 ± 3.5 | | | | |
| Turner-McGrievy Turner-McGrievy et al 2014 | Low calorie diet | 9 | 29 | -0.4 ± 0.9 | | | | |
| Chavarro Chavarro et al 2012 | Questionnaire | 170 | 30 | 8.03 (Median) IQR (-0.1, 1.8) | | | | |
| Kort Kort et al 2014 | Diet & exercise | 52 | | | 1 | -13.89% ± 3.71% in 17 with 10% weight loss -3.79% ± 3.98% in 35 with <10% weight loss | | |
| Khaskheli Khaskheli et al 2013 | Diet & exercise | 85 | | | 2 | -9.6 ± 1.23 | | |
| Lazurova Lazurova et al 2004 | Sibutramine, diet, exercise | 15 | | | 5 | -4.6 ± 4.2 (SEM) | | |
| Qublan Qublan et al 2007 | Diet | 24 | | | 6 | -4.8 | | |
| Qublan Qublan et al 2007 | Metformin | 22 | | | 7 | -4.1 | | |
| Miller Miller et al 2008 | Diet & exercise | 12 | | | 18 | -2.06 ± 0.51 (SEM) | | |
| Sonmez Sonmez et al 2005 | Acarbose | 15 | | | 22 | -1.1 ± 2.78 | | |
| Lazurova Lazurova et al 2004 | Metformin | 30 | | | 23 | -0.85 ± 0.38 (SEM) | | |
| Sonmez Sonmez et al 2005 | Metformin | 15 | | | 25 | -0.3 ± 2.47 | | |
| Homan Homan et al 2012 | Motivational interviewing | 35 | | "47% of the overweight participants had a modest loss of between 1 and 5 kg (not statistically significant)" | | | | -3.8 in 1/2 of those attending follow-up and not pregnant |
| Duval Duval et al 2015 | Diet & exercise | 24 | | 10/24 had ≥ 5% weight loss | | | | 12/24 had ≥ 5cm reduction (compared to 11/31 in control group) |

| Study ID | Intervention Arm | | Mean Weight change (kg) Per Participant | | Mean BMI change (kg/m ²) Per Participant | | Mean Waist Circumference change (cm) Per Participant | |
|---------------------------------------|--------------------------|----|---|--|--|--|--|---|
| | | N | Rank | Change | Rank | Change | Rank | Change |
| | | | | (compared to 11/31 in control group) | | | | |
| Karimzadeh et al 2010 | Diet & exercise | 75 | | | | | | Significantly lower waist circumference (P=0.001) in the lifestyle group than in the clomiphene, metformin, and clomiphene/metformin groups |
| Aliyeva et al 1993 | Diet | 60 | | "30-40% decrease in body weight in 2-4 months" | | | | |
| Aliyeva et al 1993 | Acupuncture | 20 | | "Slower rate and extent of weight reduction: 7-9 months" | | | | |
| Awartani et al 2012 | Weight reduction advised | 90 | | | | 23/90 reduced their BMI below 35; 65/90 did not | | |
| Crosignani et al 2003 | Diet & exercise | 33 | | | | | | Those with 5% weight loss had mean waist circumference 94 cm, SD 9 Those with 10% weight loss had mean 86, SD 7 |
| Van Dam et al 2004 | Very low calorie diet | 15 | | 14/15 loss at least 10% of body weight | | | | |
| Palomba et al 2008 | Exercise | 20 | | Ovulatory (n=13): Mean -5.6%, SD 1.6% Anovulatory (n=7): Mean -2.0%, SD 0.2% | | Ovulatory (n=13): Mean -10.0%, SD 3.7% Anovulatory (n=7): Mean -1.4%, SD 2.1% | | Ovulatory (n=13): Mean -9.6%, SD 2.1% Anovulatory (n=7): Mean -2.5%, -SD 2.9% |
| Palomba et al 2008 | Diet | 20 | | Ovulatory (n=5): Mean -10.5%, SD 4.1% Anovulatory (n=15): Mean -2.3%, SD 3.1% | | Ovulatory (n=5): Mean -15.4%, SD 3.9% Anovulatory (n = 15): Mean -4.0%, SD 5.2% | | Ovulatory (n=5): Mean -9.4%, SD 2.5% Anovulatory (n=15): Mean -2.8%, SD 3.1% |

Table 4. Reproductive and weight outcomes for infertile men.

| | Faure <i>Faure et al</i> 2014 N=8 | Hakonsen <i>Hakonsen et al</i> 2011 N=27 of 44 at follow-up |
|--|--|---|
| Clinical pregnancy rate | 8/8 | |
| Live birth rate | 8/8 | |
| Improvement in sperm DNA integrity | 6/6 consenting to semen analysis upon completion | |
| Change in sperm concentration (million/ml) | | Group 1 (n=9) Mean -11 95% CI -49, 27 |
| Group 1: Weight loss 3.5-12.1% | | Group 2 (n=9) Mean +19 95% CI -23, 61 |
| Group 2: Weight loss 12.2-17.1% | | Group 3 (n=9) Mean +17 95% CI -24, 58 |
| Group 3: Weight loss 17.2-25.4% | | |
| Change in sperm motility (% motile) | | Group 1 (n=8) Mean -2 95% CI -15, 11 |
| | | Group 2 (n=9) Mean +4 95% CI -10, 18 |
| | | Group 3 (n=9) Mean +11 95% CI -3, 25 |
| Change in normal sperm morphology (% normal forms) | | Group 1 (n=9) Mean 0 95% CI -2, 4 |
| | | Group 2 (n=9) Mean +1 95% CI -3, 4 |
| | | Group 3 (n=9) Mean +4 95% CI 1, 7 |
| Change in weight (kg) | Mean -4.40 SD 5.00 | Median -22 Range -4 to -39 |
| Change in BMI (kg/m ²) | Mean -1.22 SD 1.38 | |
| Change in Waist circumference (cm) | Mean -8.50 SD 7.89 | |